ENDOCRINE SOCIETY
Hormone Science to Health

**Submitted by the Endocrine Society in response to EPA-HQ-OPP-2023-0474-0005 "Endocrine Disruptor Screening Program: Near-Term Strategies for Implementation"**

February 22 2023

The Endocrine Society appreciates the opportunity to comment on near-term strategies to help the Agency meet its obligations and commitments under the Federal Food, Drug, and Cosmetic Act (FFDCA). Founded in 1916, the Endocrine Society is the world's oldest, largest, and most active organization devoted to research on hormones and the clinical practice of endocrinology. Our membership consists of over 18,000 scientists, physicians, educators, nurses, and students in more than 100 countries. Society members represent all basic, applied, and clinical interests in endocrinology. Included among our members are the world's leading experts on the health effects of endocrine-disrupting chemicals (EDCs).

**The EDSP Strategy Should Include Comprehensive Vision for Endocrine Effects**

We remain concerned that despite decades of accumulating evidence of the effects of chemicals like bisphenols, atrazine, and chlorpyrifos on endocrine systems, the Endocrine Disruptors Screening Program (EDSP) remains unable to identify risks from these and other known EDCs. Furthermore, the strategy as described remains focused on a limited number of chemicals and a select number of pathways despite growing evidence demonstrating chemical interference with retinoid signaling, peroxisome proliferator-activated receptors (PPARs), insulin receptor signaling, gastrointestinal hormones, adrenal hormones and hormones that affect or are produced by the cardiovascular system, among others[1]. This is despite the fact that these pathways are included in EPA's own ToxCast platform and Computation Toxicology program. Therefore, we do not believe that the near-term strategy as described meets today's pressing public and environmental health needs, nor is it consistent with other programs within EPA. EPA should act with greater urgency towards a vision that:

1. Assesses chemicals for effects on endocrine systems beyond estrogen, androgen, thyroid and steroidogenesis (EATS), including pathways underlying prevalent human chronic diseases.
2. Utilizes an expanded suite of more sensitive endpoints to assess endocrine disruption during important biological stages more effectively.
3. Tests a broader range of chemicals.
4. Accounts for the growing field of mixture risk assessment, especially considering the mixtures relevant to products such as pesticides.
5. Identifies cumulative risks to environmental justice communities of concern from endocrine disruption, integrating information from products regulated under the Federal Insecticide, Fungicide, and Rodenticide Act and the Federal Food, Drug, and Cosmetic Act.

[1] Martyniuk et al., Environmental Research Volume 204, Part A, March 2022, 111904

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We also do not understand EPA's decision to focus exclusively on human health data for this effort given the important foundational work on endocrine disruption in ecological contexts that is relevant to public health outcomes and the recommendation (5.8) by the National Academies report indicating that all animal data should be used for human health assessment[2]. We appreciate that EPA faces a significant challenge addressing an expanding and increasingly complex chemical environment; limiting the available data for use in this strategy appears unnecessarily restrictive and counterproductive. Better use of all available data in addition to grouping approaches e.g., read-across to apply positive hazard results from data rich chemicals, will help achieve protections that the public rightly expects. Towards this end, we also recommend that EPA use existing approaches and data gathered through other effective frameworks, such as the Integrated Risk Information System (IRIS), that already have clear policies and strategies for including New Approach Methods (NAMs) in assessment strategies.

We note that the existing battery of in vivo assays in the EDSP are now 20-50 years old and do not reflect modern or state-of-the-art scientific knowledge in the published literature on EDCs. EPA should not only seek to rebuild the EDSP, but also ensure that it can integrate new scientific approaches and knowledge into assessments. Therefore, the near-term strategy should indicate how the agency plans to improve their ability to detect EDCs within and beyond EATS through updated approaches, such as those used in the CLARITY BPA study[3], and highly sensitive endpoints such as the mammary gland[4].

**Policy Decisions Should Follow from Scientific Knowledge**

The near-term strategy appears to emphasize the role of NAMs in generating information on endocrine disruption as a policy priority; however, we do not believe that the scientific case for prioritizing NAMs relative to other testing strategies has been conclusively addressed. As currently understood, the pivot to NAMs and the prioritization of NAMs within EDSP appears to be driven by policy considerations more than science, without a clear path towards decision-making application. We are concerned that the key barriers to the regulatory adoption of NAMs as described in the NASEM report "Building Confidence in New Evidence Streams for Human Health Risk Assessment: Lessons Learned from Laboratory Mammalian Toxicity Tests[5]" remain unsolved and

[2] National Academies of Sciences, Engineering, and Medicine. 2022. New Approach Methods (NAMs) for Human Health Risk Assessment: Proceedings of a Workshop–in Brief. Washington, DC: The National Academies Press. https://doi.org/10.17226/26496.
[3] Heindel et al., Reproductive Toxicology. 2020:98 29-60
[4] Vandenberg, Adv Pharmacol. 2021:92:237-277; Kay et al., Curr Env Health Rep. 2022: 9:535-562.
[5] National Academies of Sciences, Engineering, and Medicine. 2023. Building Confidence in New Evidence Streams for Human Health Risk Assessment: Lessons Learned from Laboratory Mammalian Toxicity Tests. Washington, DC: The National Academies Press. https://doi.org/10.17226/26906.

recommendations from this report have not been well incorporated into the proposed strategy outlined for the EDSP by the EPA.

Critically, it is not clear from the strategy how EPA will make decisions using NAMs, i.e., what results will trigger a positive score, and what would be the regulatory consequences of that score. It is also unclear if a negative result from a NAM will prevent EPA from making an alternative conclusion following a positive result from a rodent study. We maintain that negative results from NAMs should not be used to invalidate positive results from animal studies, nor should they be used to downgrade a chemical's hazard assessment, but rather only to identify hazards (i.e., NAMs should improve health protection and a negative result in a NAMs test alone should never result in a conclusion that a chemical is safe). EPA should continue to work towards adoption of NASEM recommendations, including but not limited to utilizing parallel "intended target human" and "test method" PECO (population, exposure, comparator, and outcomes) statements to transparently specify the intended purpose and context of all NAMs proposed for use in human health hazard identification or dose-response assessment. EPA should also consider that recommendations from the NASEM report "Science and Decisions: Advancing Risk Assessment[6] as well as the more recent report on new evidence streams[5] be adopted in EDSP. Specifically, the EDSP needs to provide an alternative to the 'implicit' default of no data = no risk that excludes chemicals from risk assessments that lack epidemiologic or toxicologic studies and therefore assumed that they pose no hazard or risk.

EPA also lacks criteria and a systematic framework for integrating data from NAMs with the broader biomedical literature, which will be necessary to effectively use all available data to arrive at scientifically justifiable decisions. Similarly, we do not see a requirement in the strategy to validate NAMs to ensure that they are fit for the purpose of identifying EDCs and are able to effectively capture effects on endocrine systems. Such validation studies, including comparisons with assays used in academic labs to examine sensitive effects, are necessary to build trust in the EDSP and establish a scientific foundation from which to expand the use of NAMs and other studies to assess endocrine disruption. Evaluation of the scientific confidence in NAMs shall be done in a way that considers, "what choice best promotes the overall goal of protection of public health, which may differ depending on the particular context of use (e.g., filling data gap, complementing existing data, or offering an alternative)[5]." EPA should transparently describe how the NAMs will be used in regulation so that important feedback loops, developmental events, and delayed effects are captured. Furthermore, the Agency should include information on how the use of the NAMs chosen will facilitate, rather than hinder EPA's ability to account for environmentally unjust exposures that may make the hazards of a chemical a greater risk to vulnerable populations.

[6] National Research Council. 2009. Science and Decisions: Advancing Risk Assessment. Washington, DC: The National Academies Press. https://doi.org/10.17226/12209.

Therefore, it is important to prioritize the clarification of NAMs from a decision-making perspective. As a policy, EPA should recognize, as we do, that if a chemical is identified (e.g.) as a ligand for the estrogen receptor or an inhibitor of the sodium/iodide symporter, it is an intrinsic property of the chemical that is hazardous and must be recognized as such irrespective of the risk the chemical poses. In short, the absence of a risk is not the same as the absence of a hazard. We note that the key characteristics of endocrine disrupting chemicals provides a roadmap to using NAMs to identify chemical hazards[7].

**Technical Issues Require Clarification**

Our members maintain that a trusted, effective EDSP should have transparent decision-making processes that enable communities and scientists to understand the rationale behind actions taken, or not taken, by EPA. As a starting point, EPA should more clearly describe the outcomes for the chemicals that have already undergone tier 2 screening and describe how these outcomes compare to conclusions derived from academic research. We also suggest that EPA clarify how it will make decisions for chemicals such as ethylene oxide where the mechanism of action may not clearly relate to the Adverse Outcome Pathways (AOPs) in the strategy. Given the strong evidence that ethylene oxide contributes to breast cancer, EPA must show how it can screen for and identify this and similar chemicals with effects on the mammary gland. To better align the EDSP with the underlying features of interference with hormone systems, EPA should consider an approach that incorporates the Key Characteristics of EDCs[7]. Piloting this approach with the 3 chemical lists defined in the proposed near-term strategy as well as the pesticides/biocides included in the EU's Endocrine Disruptor Assessment List[8] would provide a benchmark for EDSP and clarify where data gaps exist.

For example, when hazard information exists relevant to the endocrine system, EPA should use a transparent framework to describe how risk-based decisions are made. As noted previously [5] the Key Characteristics approach can "help guide development and evaluation of the relationship between perturbations observed in assays and their potential human health hazard." This includes perturbations observed in non-mammalian assays, indicating their relevance to human health assessments. Through this approach, the Agency could for example design a strategy that organizes information already generated by manufacturers and collected by the Agency, integrating peer-reviewed scientific literature or other sources for each chemical being assessed to transparently describe the known, suspected, and unknown characterization of endocrine hazards.

Our members would also appreciate additional clarification of how the Area-Under-the-Curve (AUC) approach will deal with non-monotonic dose responses that have been observed and are to be expected based on fundamental principles of endocrinology[9] We note that EPA acknowledges the

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[7] La Merrill et al., Nat Rev Endocrinol. 2020 Jan;16(1):45-57. doi: 10.1038/s41574-019-0273-8.
[8] https://echa.europa.eu/de/ed-assessment
[9] Zoeller et al., Endocrinology. 2012 Sep;153(9):4097-110.

challenge in interpreting information using this approach, necessitating further explanation with clear examples.

**Final Recommendations for the EDSP Strategy**

In conclusion, we maintain that a forward-looking strategy is possible based on current scientific knowledge and evidence of human and ecological health effects of EDCs.

Given the scientific limitations of NAMs, EPA should clearly describe:

1. What the known limitations of NAMs are in the context of the strategy
2. What cannot be achieved using NAMs in the identification of EDCs
3. Where data gaps and uncertainties exist, and
4. How to transparently address such gaps using both NAMs and smarter use of in vivo testing.

We note that several national and international governments have prioritized efforts to identify and remove hazardous EDCs from commerce, and the United States is at risk of worse outcomes if we fail to recognize and address the threat from EDCs to public and environmental health. Indeed, public interest groups and environmental justice communities of concern have commented on the improvements needed to build trust in NAMs for use in chemical regulation, particularly for communities most impacted by chemical exposures in the US[10]. We urge EPA to expeditiously update the strategy to more fully account for the effects of chemicals on endocrine systems via systematic approaches that integrate academic data with transparent results from new assays with better sensitivity. Our members stand ready to help you in this important endeavor. If we can be of further assistance please contact Joe Laakso, PhD, Director of Science Policy at jlaakso@endocrine.org.

Sincerely,

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[10] https://www.nrdc.org/sites/default/files/2023-03/epa-letter-tsca-nams-20230315.pdf